IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Keiichi FUJIWARA et al.
Appln. No.: 10/582,174 Group Art Unit: 1612
Filed: December 7, 2004 Examiner: GIGI HUANG
For: DRUG-CONTAINING GRAINS AND SOLID PREPARATION CONTAINING THE GRAINS

DECLARATION

Commissioner for Patents
P.O. Box 1450
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Sir:

I, Norihito SHIMONO, a citizen of Japan and residing at No. 3-13, Ibukidainishi-machi 6-chome, Nishi-ku, Kobe-shi, Hyogo, Japan, declare and say as follows.

1. I was graduated from the Kyoto University, Faculty of Pharmacy, Department of Pharmaceutical Sciences, Japan in March 1986, and completed the master's course at the same university, Graduated School of Pharmaceutical Sciences in March 1988, and awarded the degree of Doctor of PH from the Kyoto University, Graduated School of Pharmaceutical Sciences in January 2003.

2. Since April 1988 up till the present, I have been an employee of Dainippon Sumitomo Pharma Company, Limited (former Dainippon Pharmaceutical Company, Limited), and I have been engaged in research work of pharmaceutical formulations in Medical Product Research Laboratory of said company.

3. I am one of the inventors of the present U.S. Patent Application No. 10/582,174 and am familiar with the present invention.

4. Based upon my knowledge and experience in the drug formulation fields, I can say as follows.

5. The present invention is a medicament-containing particle which is obtainable by mixing and granulating a composition comprising (1) the medicament with an unpleasant taste, (2) methylcellulose, and (3) mannitol. And, by restricting the amounts of the methylcellulose and mannitol to the predetermined ranges, the unpleasant taste of the medicament can be alleviated without any special technique such as coating and microcapsulation. The masking of the unpleasant taste without coating or microcapsulation technique is the greatest property of the present invention. The particle of the present invention can be incorporated into various solid preparations.

6. On the other hand, I have read the cited Siebert et al. US 6,368,625 and I know well the contents of the U.S. patent.

7. The invention disclosed in the cited Siebert et al. reference (US 6,368,625 B1) is intended to orally disintegrable dosage forms for the delivery of sustained or extended release microcapsules and/or prompt release coated or non-coated drug particles (see column 1, lines 9-12 in US 6,368,625 B1). The citation also discloses that the tablet has a property to be easy and pleasurable to swallow (see column 3, lines 8-9 therein). The property might be thought as a kind of masking taste. However, the technique of masking taste is via a coating or microcapsulation technique, which is quite different from that of the present invention.

8. In addition, the cited Siebert et al. reference discloses in Example 1 a formulation comprising a medicament (famotidine), mannitol, microcrystalline cellulose, and so on. Therefore, Mr./Ms. Examiner indicates that it would have been obvious for a skilled person in the art to substitute microcrystalline cellulose with methylcellulose to produce the present invention. Actually, methylcellulose is generally used as a binder like microcrystalline cellulose and also Siebert et al. reference teaches the preferred binders include microcrystalline cellulose and methylcellulose (provided that there was no working example using methylcellulose in the cited Siebert et al. reference). However, the present inventors including me have found that the use of methylcellulose in the composition of the present invention can bring about the useful masking taste. I believe that the use of microcrystalline cellulose or other celluloses such as

hydroxypropyl cellulose and hydroxypropyl methylcellulose could not bring about such excellent masking effect like the case using methylcellulose. In order to prove what I insist herein about the relationship between methylcellulose and masking taste, I and co-researchers have carried out the following comparative experiment.

9. As shown in the following Tables 1 and 2, two different particles were prepared and then examined about masking taste. The composition of Particle 1 comprises famotidine, D-mannitol and microcrystalline cellulose whose amounts correspond to the ratio described in Example 1 of the cited Siebert et al. reference, while the composition of Particle 2 was prepared by substituting microcrystalline cellulose of Particle 1 with methylcellulose. The preparation of the two particles was carried out according to the process described in the present description (the detailed process was described beneath Table 1).

Table 1

	Particle 1	Particle 2
Famotidine	3.03 g (4.8 %)	3.03 g (4.8 %)
D-mannitol	50.37 g (79.5 %)	50.37 g (79.5 %)
Microcrystalline cellulose	10.00 g (15.8 %)	—
Methylcellulose	—	10.00 g (15.8 %)
Purified water	moderate amount	moderate amount
Total (solid component)	63.4 g (100 %)	63.4 g (100 %)

<Preparation>

All the ingredients listed as each particle in Table 1 were mixed and granulated in an agitating granulator (DALTON, YM-Q-7) while dropping purified water , and then dried in a tray type dryer. The resulting granules were sifted by means of a 32 mesh sieve (opening, 500 μm) to give medicament-containing particles whose average particle size is about 100 μm.

10. Using the two kinds of particles prepared above, the masking effect was evaluated. The evaluation method is as follows:

Each particle (wherein the amount of famotidine is 20 mg) was set on each tongue of three healthy adult men selected as a subject, the particle was held in his closed mouth for 30 seconds without chewing,

then the particle was disgorged out of his mouth, and the feeling in mouth of each subject was evaluated with the following 5 grades and the score was recorded. The result is shown in the following Table 2 (the worst score is shown as a result).

Table 2

	Masking degree of the unpleasant taste
Particle 1	△
Particle 2	◎

◎: Masking effect was clearly exhibited and the unpleasant taste was not felt at all.

○: Masking effect was exhibited, and the unpleasant taste was almost masked and was not actually felt.

△: Masking effect was exhibited and the unpleasant taste was not almost felt.

×: Masking effect was somewhat exhibited, but the unpleasant taste was felt.

××: There was no masking effect and the unpleasant taste was felt.

11. As clearly shown in Table 2, Particle 2 containing methylcellulose exhibits more marked masking effect of the unpleasant taste than Particle 1. This effect in Particle 2 which is the present invention is unpredictable/unexpected based on the cited Siebert et al. reference.

12. In addition, in order to make it clear that the masking effect of the present invention is effective for any medicaments having unpleasant taste other than "mosapride citrate" which is a medicament tested in the present description, I and co-researchers prepared the following 8 particles shown in Tables 3 and 4 which are in the range of the present invention using 8 medicaments having unpleasant taste (famotidine, acetaminophen, metformin hydrochloride, omeprazole, lansoprazole, Excegran®, ethenzamide, ibuprofen) by means of the above process method in Table 1, and evaluated about masking effect by means of the above method in Table 2. The result is shown in Table 5.

Table 3

Particle		3	4	5	6
Medicament	Famotidine	6 g (10 %)	—	—	—
	Acetaminophen	—	6 g (10 %)	—	—
	Metformin hydrochloride	—	—	6 g (10 %)	—
	Omeprazole	—	—	—	6 g (10 %)
D-mannitol		42 g (70 %)	42 g (70 %)	42 g (70 %)	42 g (70 %)
Methylcellulose		12 g (20 %)	12 g (20 %)	12 g (20 %)	12 g (20 %)
Purified water		moderate amount	moderate amount	moderate amount	moderate amount
Total (solid component)		60 g (100 %)	60 g (100 %)	60 g (100 %)	60 g (100 %)

Table 4

Particle		7	8	9	10
Medicament	Lansoprazole	6 g (10 %)	—	—	—
	Excegran®	—	6 g (10 %)	—	—
	Ethenzamide	—	—	6 g (10 %)	—
	Ibuprofen	—	—	—	6 g (10 %)
D-mannitol		42 g (70 %)	42 g (70 %)	42 g (70 %)	42 g (70 %)
Methylcellulose		12 g (20 %)	12 g (20 %)	12 g (20 %)	12 g (20 %)
Purified water		moderate amount	moderate amount	moderate amount	moderate amount
Total (solid component)		60 g (100 %)	60 g (100 %)	60 g (100 %)	60 g (100 %)

Table 5

Particle	Masking degree of the unpleasant taste
3	○
4	○
5	○
6	○
7	○
8	○
9	◎
10	◎

13. As clearly shown in Table 5, the masking effect of the present invention can be exhibited in every particle using various medicaments having unpleasant taste.

14. In conclusion, it is definite that the present invention cannot be thought up based on the cited Siebert et al. reference as you can see from the result of the above comparative experiment in Tables 1 - 2. I believe that it is impossible even for a skilled person to think up the marked masking effect of the present invention via substituting microcrystalline cellulose in the cited Siebert et al. reference with methylcellulose.

15. It is my opinion, based upon my knowledge and experience in this field, the particle of the present invention which is obtainable by mixing and granulating a composition comprising (1) the medicament with an unpleasant taste, (2) methylcellulose, and (3) mannitol is very excellent because the particle enables a masking of unpleasant taste just by restricting the amounts of the methylcellulose and mannitol to the predetermined ranges and it is not necessary to use <u>any special technique such as coating and microcapsulation</u>. In addition, as you can see from the result of the above complementary experiment in Tables 3 - 5, the present invention can be adapted to every medicament having unpleasant taste. I believe that such useful invention like this which enables a masking of unpleasant taste by such simple means had not been known before.

16. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 14th day of May, 2009

Norihito Shimono

Norihito SHIMONO, Ph.D.